Generating Data for the Development and Validation of Biologically Based Dose-response Models

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Extrapolations of animal cancer data to human risks at occupational exposures have several inherent assumptions because our understanding of mechanisms of carcinogenicity is incomplete and because there is generally insufficient information on the distribution of risk factors in exposed workers. The advancement of scientific knowledge of critical steps in chemical carcinogenesis in laboratory animals and humans may eventually obviate the need for many default assumptions. The development of biologically based dose-response (BBDR) models offers a mechanism-based approach to replace assumptions with valid scientific data. BBDR models allow quantification of time-dependent relationships between exposure and target tissue dose and consequent changes in biochemical processes that result in the tissue response. In addition, these models can address multiple routes and patterns of exposure experienced by workers, accommodate parameter values that encompass the range of human variability in susceptibility (e.g., differential expression of genes that code for enzymes involved in metabolic activation or detoxication or genes that control DNA repair), and can be used to test purported biological mechanisms or modes-of-action.

To account for potential differences in susceptibility between species and among various human subgroups, as well as differences in exposure circumstances, species-specific information at the cellular and molecular levels will be critical for the development of models that can be used to quantify relationships between time-dependent target tissue dose and tissue response as a function of exposure to carcinogenic agents in the workplace. BBDR models combine toxicokinetic data on the absorption, distribution, metabolism, and elimination of agents at different levels of exposure with mechanistic data of time-dependent tissue response (e.g., mutagenicity, altered gene expression). Species-specific mechanistic data, including parameters that are measurable in humans, are critical for the development of these models. Experimental data are needed to estimate relevant parameter values (e.g., tissue partition coefficients, enzymatic activities, binding constants) and to resolve uncertainties in the accuracy of parameter estimates, interdependence of parameters, validity of scaling methods, variability of parameters among individuals, and effects of coexposure to other agents that may alter any of the critical biological processes. These models should evaluate similarities and differences in animal and human response as a function of the time-dependent tissue dose, whether the correct dose metric(s) have been specified for extrapolations, and whether responses in animals reflect the range of responses that might occur in exposed workers.

Information in the literature can be used to provide a structural framework that realistically represents processes regulating the biological behavior of various agents under study and to obtain several of the physiological and biochemical parameters that correspond to these processes in animals and humans. Additional data are needed to adequately account for interspecies, intraspecies, and sex differences in susceptibility, including the timing and duration of exposure, age, race, tumor latency, exposure to other agents, route(s) of exposure, health status, lifestyle, and the multitude of relevant hormonal and genetic factors. Model development is an information generating iterative process that integrates all available data on the behavior of

the agent in tissue samples (including in vitro or animal models and in humans) and that builds on our rapidly expanding knowledge of the cellular and molecular events that contribute to the carcinogenic processes. This iterative process involves designing experiments, confirming that predictions reproduce experimental data, and evaluating the consistency of alternative mechanistic hypotheses. Hence, development of credible BBDR models requires collaborative interactions between modelers and experimentalists.

Biological models that address mechanistic steps linking exposure to adverse effects offer an objective, data-based approach to test biologically based hypotheses and to generate alternative hypotheses for laboratory testing. If mechanistic hypotheses are not adequately tested in an appropriate dose-response framework, then approaches to estimate occupational risks that rely on such hypotheses may simply be replacing one set of assumptions for another where the latter set may not provide adequate health protection. Properly validated models (i.e., those most consistent with the experimental data) should accurately predict measured biomarkers of exposure and biomarkers of effect. By linking the sequence of events between exposure and response, BBDR models can provide mechanistic insights on the origin of biological changes that occur at the cellular and molecular levels in the induced carcinogenic response and help identify specific biomarkers that are appropriate measures of exposure, effect, and/or susceptibility. Validated BBDR models can provide a sound scientific basis for extrapolating dose-response relationships across species and outside the range of experimental observation and thus reduce uncertainties in estimating human risk.